Amendments to the Specification

Please delete the paragraph on page 3, line 31, to page 4, line 13, and replace it with the following paragraph:

As referred to herein, a repetitive element is a nucleotide sequence (or other similar term) of an oligonucleotide that will start and end with a nucleotide having the same nucleobase substitution (e.g. G) and within those start and end nucleotides most of the contained nucleotides will have the same nucleobase substitution as the start and end nucleotides. Preferably, inclusive of the start and end nucleotides, a repetitive nucleotide sequence of an oligonucleotide will have at least about 60, 70 or 80 percent of the total nucleotides of the sequence having the same nucleobase substitution (e.g. at least 60, 70, or 80 percent of the total nucleotides all will have G substitution). More preferably, 90 percent, 95 percent or all of the nucleotides of the repetitive sequence will have the same nucleobase substitution. Preferred examples of repetitive elements are a homopolymeric nucleotide sequence, such as a poly(A) tail of eucaryotic mRNA, or a conserved repetitive element or a conserved sequence, e.g. of a ribosomal RNA sequence. Said repetitive elements may comprise a minor proportion of other nucleobases or analogues thereof, e.g. the sequence 5'-aaaaagaaaaaaa-3' (SEQ ID NO: 18), without substantially affecting the overall homopolymeric nature of the nucleotide sequence.

Please delete the paragraph on page 9, lines 16-20, and replace it with the following paragraph:

Figure 1 is a graph showing the percent recovery of yeast in vitro-transcribed *ACT1* mRNA using LNA/DNA capture probes at varying hybridization temperatures using a buffer containing a chaotropic agent (4M GuSCN). The biotinylated oligo-T capture probes used are shown in the top panel (see SEQ ID NOS 5, 4, 2, 3 and 1, respectively). The percent recovery was calculated from gel electrophoresed dilution series of an RNA standard.

Please delete the paragraph on page 9, lines 22-26, and replace it with the following paragraph:

Figure 2 is a graph showing the percent recovery of yeast in vitro-transcribed *SSA4* mRNA using LNA/DNA capture probes at varying hybridization temperatures using a buffer containing a chaotropic agent (4M GuSCN). The biotinylated oligo-T capture probes used are shown in the top

panel (see SEQ ID NOS 5, 4, 2, 3 and 1, respectively). The percent recovery was calculated from gel electrophoresed fragments.

Please delete the paragraph on page 9, lines 28-31, and replace it with the following paragraph:

Figure 3 is a graph showing the percent recovery of yeast *ACT1* mRNA using LNA/DNA capture probes at varying hybridization temperatures using a high salt buffer 0.5 M NaCl.The biotinylated oligo-T capture probes used are shown in the top panel (see SEQ ID NOS 5, 4, 2, 3 and 1, respectively). The percent recovery was calculated from gel electrophoresed fragments.

Please delete the paragraph on page 10, lines 1-3, and replace it with the following paragraph:

Figure 4 is a graph showing biotin-labeled LNA/DNA capture probes (see SEQ ID NOS 1, 3, 6, 7, 9 and 10, respectively) immobilized on a streptavidin-coated EURAY™ polymer slide and hybridized to 0.1 μM Cy5-oligo-dT_{20} (SEQ ID NO: 1).

Please delete the paragraph on page 10, lines 5-7, and replace it with the following paragraph:

Figure 5 is a graph showing biotin-labeled LNA/DNA capture probes (see SEQ ID NOS 1, 3, 6, 7, 9 and 10, respectively) immobilized on a streptavidin-coated EURAY™ polymer slide and hybridized to 0.1 μM Cy5-oligo-dT_{20} (SEQ ID NO: 1) in 4 M GuSCN buffer.

Please delete the paragraph on page 10, lines 9-11, and replace it with the following paragraph:

Figure 6 is a gel (left panel) and a graph (right panel) showing the recovery of in vitro-transcribed yeast SSA4 mRNA in different concentrations of guanidinium thiocyanate (GuSCN). DNA_dT_{20} and LNA_2.T are shown in SEQ ID NOS 1 and 2, respectively.

Please delete the paragraph on page 10, lines 25-31, and replace it with the following paragraph:

Figures 9A and B show capture of SSA4 spike mRNA by AQ-coupled LNA oligo-T capture probes (see SEQ ID NOS 1, 2, 11, 12, 13, 14, 15 & 1, and 15 & 2, respectively). Solid lines represent LNA capture probes and stipple lines control DNA capture probes. The linker constructions are

demonstrated by the following symbols: Diamonds depict AQ_2-HEG_3-, triangles denoe AQ_2-t15- (SEQ ID NO: 16), squares depict AQ_2-c15- (SEQ ID NO: 17), and circles AQ_2-t10-NB5- (SEQ ID NO: 15). Figure 9A demonstrates detection using an LNA probe for SSA4 spike mRNA. Figure 9B demonstrates detection using a DNA probe for SSA4 spike mRNA.

Please delete the paragraph on page 10, line 33, to page 11, line 3, and replace it with the following paragraph:

Figure 10 shows titration of polyadenylated SSA4 mRNA captured by AQ-coupled oligo-T capture probes (see SEQ ID NOS 1, 2, 11, 12, 13, 14, 15 & 1, and 15 & 2, respectively). Solid lines LNA capture probes and stipple lines control DNA capture probes. The linker constructions are demonstrated by the following symbols: Diamonds denote AQ_2-HEG_3-, triangles denote AQ_2-t15- (SEQ ID NO: 16), squares depict AQ_2-c15- (SEQ ID NO: 17), and circles depict AQ_2-t10-NB5- (SEQ ID NO: 15).

Please delete the paragraph on page 11, lines 5-7, and replace it with the following paragraph:

Figure 11 shows isolation of poly(A)$^+$RNA from heat shocked wild type yeast total RNA followed by specific detection of the SSA4 mRNA using a biotinylated SSA4-specific detection probe (see SEQ ID NOS 1, 2, 11, 12, 13, 14, 15 & 1, and 15 & 2, respectively).

Please delete the paragraph on page 11, lines 9-11, and replace it with the following paragraph:

Figure 12 shows recovery of ACT1 in vitro spike mRNA after hybridisation in different NaCl-salt concentrations. DNA oligo-dT (open bars, SEQ ID NO: 1) and LNA oligo-T (solid bars, SEQ ID NO: 2).

Please delete the paragraph on page 11, lines 13-17, and replace it with the following paragraph:

Figure 13 shows quantification of isolated poly(A)$^+$RNA from C. elegans worms, analysed by native agarose gel eletrophoresis as captured by either the LNA_2.T (SEQ ID NO: 2)(solid bars) or

DNA-dt_{20} (SEQ ID NO: 1) (open bars) capture probes. The hatched bar indicates a negative control performed without oligo-T capture probe during the isolation the poly(A)$^+$RNA.

Please delete the paragraph on page 11, lines 19-21, and replace it with the following paragraph:

Figure14 shows Northern blot analysis of poly(A)$^+$RNA isolated from increasing amounts of *C. elegans* worm extracts probed with 32P-labeled fragments for the *C. elegans* genes RPL-21 and 26S rRNA, respectively. DNA_dT_{20} and LNA_2.T are shown in SEQ ID NOS 1 and 2, respectively.

Please delete the paragraph on page 16, line 27, to page 17, line 7, and replace it with the following paragraph:

In a preferred embodiment, the LNA oligomers comprise a repeat element of the following:

5'- Y^q-(X^p –Y^n)$_m$-X^p-Z-3'

wherein X is an LNA monomer, Y is a DNA monomer; Z represents an optional DNA monomer ; p is an integer from about 1 to about 15; n is an integer from about 1 to about 15 or n represents 0; q is an integer from about 1 to about 10 or q = 0; and m is an integer from about 5 to about 20. By way of example:

5'-TttTttTttTttTtt-3' (SEQ ID NO: 19)

wherein T = LNA thymidine analogue, t = DNA thymidine.

5'-GggGggGggGggGgg-3' (SEQ ID NO: 20)

wherein G = LNA guanidine analogue, g = DNA guanidine.

Please delete the paragraph on page 17, lines 9-21, and replace it with the following paragraph:

The LNA oligomers can be comprised of a repeating sequence of thymidines with a guanine or any other nucleobase located in any position of the oligomers. As an illustrative example which is not meant to limit or construe the invention in any way the LNA oligomers can be selected from Table 3 and may optionally comprise a G, A, U or C in any position of the oligomers. For example:

5'-GttTttTttTttTtg-3' (SEQ ID NO: 21)

wherein G = LNA guanidine analogue, T = LNA thymidine analogue, t = DNA thymidine, g = DNA guanidine.

5'-TttTttTttTttTgt-3' (SEQ ID NO: 22)

wherein T = LNA thymidine analogue, t = DNA thymidine, g = DNA guanidine.

Please delete Table 1 on page 51 and replace it with the following Table:

Table 1

Comp. No.	Oligo Name:	Sequence 5'-:
1	DNA_dT_{20}	5'-biotin-tttttttttttttttttttt (SEQ ID NO: 1)
2	LNA_2.T	5'-biotin-TtTtTtTtTtTtTtTtTtTt (SEQ ID NO: 2)
3	LNA_3.T	5'-biotin-TttTttTttTttTttTttTt (SEQ ID NO: 3)
4	LNA_T_{10}	5'-biotin-TTTTTTTTTT (SEQ ID NO: 4)
5	LNA_T_{15}	5'-biotin-TTTTTTTTTTTTTTT (SEQ ID NO: 5

Note: LNA nucleotides are indicated with uppercase letters, DNA nucleotides are indicated by lowercase letters. C^{met} indicates 5-methyl cytosine LNA; 5'-biotin indicates 5' biotin-$(CH_2)_4$-CONH-$(CH_2)_6$-.

Please delete the paragraph on page 51, line 18 to page 52, line 6, and replace it with the following paragraph:

Melting experiments in solution. The melting of the duplexes either LNA/DNA or DNA/DNA (control) were studied measuring absorbance (λ=260) as a function of temperature from 10°C to 90°C with an increase of 1°C/min in a Perkin-Elmer λ-40 spectrophotometer equipped with a Peltier element controlling the temperature. Hybridization mixtures of 500 µL were prepared in 10 mM sodium phosphate buffer pH 7.0 100 mM NaCl, 0.1 mM EDTA containing equimolar (1 µM) amounts of the different LNA or DNA oligonucleotides and the complementary DNA oligo-dA_{21} (SEQ ID NO: 43) or RNA oligo-rA_{20} (SEQ ID NO: 44). All melting curves were monophasic and sigmoid and the melting temperature (T_m) was obtained as the maximum of the first derivative

(d(A260)/dT) of the melting curve (A260 vs. temperature). All LNA oligonucleotides obtained higher T_m values compared to the control DNA (see table 2). The higher number of LNA nucleotides in the oligonucleotide the higher ΔT_m.

Please delete Table 2 on page 52 and replace it with the following Table:

Table 2

Comp. No:	Oligo Name:	Sequence 5'-:	T_m/°C (DNA)	ΔT_m/°C (DNA)	T_m/°C (RNA)	ΔT_m/°C (RNA)
1	DNA_T_{20}	5'-biotin-ttttttttttttttttttt (SEQ ID NO: 1)	43.7	-	40.3	-
3	LNA_3.T	5'-biotin-TttTttTttTttTttTttTt (SEQ ID NO: 3)	58.4	14.7	60.8	20.5
6	LNA_4.T	5'-biotin-ttTttTtttTttTtttTt (SEQ ID NO: 6)	51.0	7.3	56.9	16.6
7	LNA_5.T	5'-biotin-tttTttttTtttTttttTt (SEQ ID NO: 7)	47.8	4.1	52.0	11.7
4	LNA_T_{10}	5'-biotin-TTTTTTTTTT (SEQ ID NO: 4)	83.6	39.3	76.3	36.0
5	LNA_T_{15}	5'-biotin-TTTTTTTTTTTTTTT (SEQ ID NO: 5)	>95	>51.3	94.6	54.3
8	LNA_T_{20}	5'-biotin-TTTTTTTTTTTTTTTTTTT (SEQ ID NO: 8)	>95	>51.3	>95	>54.7
9	LNA_TT	5'-biotin-ttTTttTTttTTttTTt (SEQ ID NO: 9)	59.9	16.2	63.2	22.9
10	LNA_TTT	5'-biotin-ttTTTttttTTTttttTTTt (SEQ ID NO: 10)	66.3	22.6	65.2	24.9

Note: LNA nucleotides are indicated with uppercase letters, DNA nucleotides are indicated by lowercase letters. C^{met} indicates 5-methyl cytosine LNA; 5'-biotin indicates 5' biotin-$(CH_2)_4$-CONH-$(CH_2)_6$-.

Please delete the paragraph on page 53, lines 9-27, and replace it with the following paragraph:

Euray™ polymer slides were coated with 20 µg/mL streptavidin, Prozyme, (cat. no. PZSA20) in phosphate saline buffer (PBS, pH 7, 0.15 M Na^+) for 22 hours at 4°C in a humidity chamber. The slides were washed three times in PBS and briefly in demineralized water and dried for 5 min. The

slides were spotted using 10 μM of LNA or DNA oligonucleotides (table 1, table 2). The array setup: biotinylated oligonucleotides were spotted in duplicate and three times 300 pL per spot with a distance of 300 μm between spots. The slides were incubated O/N at 4°C in a humidity chamber to allow binding of biotin to the streptavidin. The slides were hybridized with 0.1 μM Cy5-oligo-dT_{20} (SEQ ID NO: 1) in either 1 x SSCT (150 mM NaCl, 15 mM Na-citrate, pH 7.0, 0.1% Tween 20) or GuSCN buffer (4 M GuSCN, 100 mM sodium phosphate buffer pH 7.0, 0.2 mM EDTA) for 2 hours at room temperature. The slides were washed in the same buffer used for hybridization. The slides were mounted with degassed hybridization buffer using a glass coverslip and nail polish for sealing and data was collected. Results show that signals from the LNA oligonucleotides are higher than the signal from the control DNA oligonucleotide when the hybridization is performed in 1 x SSCT buffer (Figure 12). However, when the hybridization is performed in the GuSCN no signal is obtained from the DNA control (figure 5). Surprisingly LNA oligonucleotides perform as well in the SSCT buffer as in the GuSCN (Figures 1, 2, 3).

Please delete the paragraph on page 55, lines 17-21, and replace it with the following paragraph:

The recovery of *in vitro* mRNA in 0 0.5, 1, 2, and 4 M GuSCN containing buffer shows that the DNA_dT_{20} (SEQ ID NO: 1) capture probe has it optimum at 0.5 M GuSCN buffer (figure 6). The LNA_2.T capture probe has it optimum at 2 M GuSCN but maintain the same recovery efficiency at 4 M GuSCN compared to the DNA_dT_{20} (SEQ ID NO: 1) capture probe.

Please delete Table 3 on page 55 and replace it with the following Table:

Table 3

Comp. No.	Oligo Name:	Sequence 5'-:
1	DNA_dT_{20}	5'-biotin-tttttttttttttttttttt (SEQ ID NO: 1)
2	LNA_2.T	5'-biotin-TtTtTtTtTtTtTtTtTtTt (SEQ ID NO: 2)

Please delete the paragraph on page 58, lines 1-15, and replace it with the following paragraph:

In an Eppendorf tube 100 µg yeast total RNA (from *Saccharomyces cerevisiae*) was prepared in a final volume of 50 µL DEPC-treated H_2O. 50 µL 2× binding buffer (20 mM Tris-HCl (pH 7.0, Ambion, USA), 0.2 M NaCl (Ambion, USA), 1 mM EDTA (pH 8.0, Ambion, USA) 0.1% ($^{w}/_{v}$) lauryl sarcosinate (Sigma, USA) was added and vortexed briefly. The biotinylated LNA oligo(T) capture probe (5'-biotin-C6-TtTtTtTtTtTtTtTtTtTt-3' (SEQ ID NO: 23); T = LNA thymine and t = DNA thymine) was added to the sample preparation together with the pre-blocked streptavidin-coated magnetic particles and allowed hybridization for 10 minutes at 37°C shaking (400 rpm in an Eppendorf Thermomixer (Radiometer, Denmark)). The particles were collected using a magnetic particle separator (Roche, USA) and the supernatant removed. The particles were washed three times in 100 µL wash buffer (20 mM Tris-HCl (pH 7, Ambion, USA), 0.05 M NaCl (Ambion, USA), 1 mM EDTA (pH 8.0, Ambion, USA) 0.1%(w/v) lauryl sarcosinate (Sigma, USA)). Finally, the poly(A)$^{+}$RNA was eluted form the particles by adding 50 µL DEPC-H_2O (Ambion Cat. no. 9924), heated for 10 minutes at 65°C and quenched on ice for10 minutes.

Please delete the paragraph on page 58, lines 19-30, and replace it with the following paragraph:

After the RNA isolation by the LNA oligo(T) capture probes 100 ng polyadenylated RNA was primed with 5 µg oligo-dT_{12-18} primer (SEQ ID NO: 24) (Amersham Biosciences) and heated 10 min at 70°C and quench on ice. The mixture was transferred to 20 µL cDNA synthesis reaction containing 50 mmol/L Tris-HCl (pH 8.3 at room temperature), 75 mmol/L KCl, 3 mmol/L $MgCl_2$, 10 mmol/L DTT (Invitrogen, USA), 1 mmol/L of each dATP, dCTP, dGTP, and dTTP (Amersham Biosciences, USA), 20U Superasin (Ambion, USA) and incubate 5 min at 37°C. 200U SuperScript™ II RT (Invitrogen, USA) was added and incubated 30 min at 37°C and 30 min at 42°C. Additional 200U of SuperScript™ II RT was added and the incubation time at 42°C was prolonged for one hour. Finally, the reaction was heated 5 min at 70°C and primers removed on a Sephacryl S-400 HR spin column (Pharmacia, USA) according to the manufacturer's recommendations.

Please delete the paragraph on page 58, line 32, to page 59, line 18, and replace it with the following paragraph:

The relevant cDNA fragment was amplified from first strand cDNA using specific primer sets for *S. cerevisiae ACT1* and *HSP78* genes, respectively. PCR reactions (50 µL) were prepared by mixing 15 mmol/L Tris-HCl, pH 8.0, 50 mmol/L KCl (GeneAmp Gold buffer, PE Biosystems); 2.5 mmol/L $MgCl_2$; 200 µmol/L of each dATP, dCTP, dGTP and dTTP (Amersham Pharmacia Biotech, USA); 0.4 mmoL/ forward primer (DNA technology, Denmark); 0.4 mmol/L reverse primer (DNA Technology, Denmark); 1.25 U (0.25 µL of a 5U/µl) AmpliTaq Gold polymerase (PE Biosystems, USA) and cDNA as template. After an initial 5 min denaturation step at 95°C, 25 cycles of PCR were carried out (60 s at 95°C, 60 s at 60°C and 60 s at 72°C), followed by extension at 72°C for 10 min. The amplicons were analysed by native agarose gel electrophoresis. The specific primer sets were: *ACT1*:

5'-ACGTGAATTCTTTCCATCCAAGCCGTTTTG3' (SEQ ID NO: 25)
and
5- -GATCCCCGGGAATTGCCATGTTAGAAACACTTGTGGTGAACGA-3'
(SEQ ID NO: 26),
HSP78: 5'-ACGTGAGCTCTTTTGACATGTCAGAATTTCAAG-3'
(SEQ ID NO: 27)
and
5 '-GATCCCCGGGAATTGCCATGTTACTTTTCAGCTTCCTCTTCAAC-3'
(SEQ ID NO: 28).

Please delete the paragraph header on page 61, lines 5-6, and replace it with the following paragraph header:

Example 8. Isothermal RNA amplification using T7 anchored LNA-$(T)_{20}$vn primer (SEQ ID NO: 45).

Please delete the paragraph on page 62, lines 10-22, and replace it with the following paragraph:

Amplification of the yeast HSP78 gene fragment was done by standard PCR using yeast genomic DNA as template. In the first step of amplification, a forward primer containing a restriction enzyme site and a reverse primer containing a universal linker sequence were used. In this step 20 bp

was added to the 3'-end of the amplicon, next to the stop codon. In the second step of amplification, the reverse primer was exchanged with a nested primer containing a poly-T_{20} **(SEQ ID NO: 1)** tail and a restriction enzyme site. The HSP78 amplicon contains 736 bp of the *HSP78* ORF plus 20 bp universal linker sequence and a poly-A_{20} (SEQ ID NO: 34) tail.

The PCR primers used were;
YDR258C-For-SacI: acgtgagctcttttgacatgtcagaatttcaag (SEQ ID NO: 29)
YDR258C-Rev-Uni: gatccccgggaattgccatgttacttttcagcttcctcttcaac (SEQ ID NO: 30)
Uni-polyT-BamHI: acgtggatcctttttttttttttttttttttgatccccgggaattgccatg (SEQ ID NO: 31),

Please delete the paragraph on page 63, lines 10-20, and replace it with the following paragraph:

One µg *in vitro* HSP78 spike mRNA was used as template and the MessageAmp™ aRNA kit (Ambion, USA) was used for cRNA synthesis. according to the manufacturer's instructions, except that 50 µM final concentration of unique T7 oligo(dTt_{10}vn) primer (SEQ ID NO: 32) was used instead of the primer from the kit. The sequence of the unique primer is 5'-ggccagtgaattgtaatacgactcactatagggaggcggTtTtTtTtTtTtTtTtTtTtvn-3' (SEQ ID NO: 33). Before ncRNA purification (according to manufacturer's instructions), the double-stranded cDNA template was removed from the reaction mixture by DNase I treatment for 30 min. at 37°C. The yield of the resulting cRNA (Table I) was measured using a Nanodrop spectrophotometer (Nanodrop, USA) and the quality of the in vitro synthesized spike RNA was assessed by gel electrophoresis on a 1% agarose gel.

Please delete Table 4 on page 63 and replace it with the following Table:

Table 4. The yield of HSP78 cRNA using a T7 anchored LNA-$(T)_{20}$vn primer (SEQ ID NO: 45).

	Input HSP78 template RNA	Yield of HSP78 cRNA
RNA	1.00 µg	18.80 µg

Please delete the paragraph on page 64, lines 16-25, and replace it with the following paragraph:

Genomic DNA was prepared from a wild type standard laboratory strain of *S. cerevisiae* using the Nucleon MiY DNA extraction kit (Amersham Biosciences, USA) according to the supplier's instructions. Amplification of partial yeast genes was performed by standard PCR using yeast genomic DNA as template. In the first step of amplification, a forward primer containing a restriction enzyme site and a reverse primer containing a universal linker sequence were used. In this step 20 bp was added to the 3'-end of the amplicons, next to the stop codon. In the second step of amplification, the reverse primer was exchanged with a nested primer containing a poly-dT_{20} (SEQ ID NO: 1) tail and a restriction enzyme site. The SSA4 PCR amplicon contains 729 bp of the *SSA4* ORF plus a 20 bp universal linker sequence and a poly-dA_{20} (SEQ ID NO: 34) tail.

Please delete the paragraph on page 64, line 27, to page 65, line 2, and replace it with the following paragraph:

The PCR primers used were;

YER103W-Rev-Uni:

5'-GATCCCCGGGAATTGCCATGCTAATCAACCTCTTCAACCGTTGG-3'

(SEQ ID NO: 35),

YER103W-For-SacI:

5'-ACGTGAGCTCATTGAAACTGCAGGTGGTATTATGA-3'

(SEQ ID NO: 36),

Uni-polyT-BamHI:

5'-A CGTGGATCCTTTTTTTTTTTTTTTTTTTTGATCCCCGGGAATTGCCATG-3'
(SEQ ID NO: 37).

Please delete the paragraph on page 65, lines 13-25, and replace it with the following paragraph:

Fifty nanograms (ng) of the *in vitro* polyadenylated *SSA4* mRNA was diluted in the guaninidinium thiocyanate (GuSCN) buffer (4 mol/L GuSCN (Sigma), 25 mmol/L sodium citrate (JT Baker), pH 7.0, 0.5 g/100 mL sodium N-lauroyl sarcosinate (Sigma, USA)). The mixture was heated to 65°C 10 minutes and quenched on ice. The SSA4 mRNA solution was dispersed into the wells by adding 50 ng SSA4 spike mRNA in 100 µL per well and incubated for 15 minutes at room temperature. The microtiter wells were washed three times in wash buffer (0.05 mol/L NaCl 20 mmol/L Tris-HCl, pH 7.6, 1 mmol/L EDTA, pH 8, 0.1g/100 mL sodium N-lauroyl sarcosinate). The detection was carried out by either a biotinylated DNA (biotin-C_6-aatcttcccttatcgttagtaattgtaatcttgtt (SEQ ID NO: 38); DNA in lower cases)

or LNA detection probe

(biotin-C_6-AatmCttmCccTtaTcgTtaGtaAttGtaAtcTtgTt (SEQ ID NO: 39);

DNA in lower case and LNA in upper case).

Please delete the paragraph on page 66, lines 6-24, and replace it with the following paragraph:

Figure 9A demonstrates the detection of the *SSA4* spike mRNA when the polyA::oligoT capture is performed in 4M GuSCN buffer and high stringency washes employing the different LNA oligo-T capture probes combined with a SSA4-specific LNA detection probe. In contrast, the control DNA oligo-(dT) capture probes do not show any detection signals under these assay conditions. When the DNA detection probe (Figure 9B) is used instead of LNA probe to detect the captured SSA4 spike RNA, low SSA4 signals were detected from the LNA-T capture probes only, while no signals were obtained from the DNA (dT) control probes. It should be noted that the DNA detection probe hybridises only weakly to its target under the high stringency hybridisation conditions used here. In conclusion, only LNA oligo-T capture probes are able to capture polyadenylated RNA in 4M guanidinium thiocyanate hybridisation buffer. Furthermore, when high stringency hybridization conditions (0.05 M NaCl) are used for detection of the SSA4 spike mRNA, only the LNA detection probe is able to hybridise and detect the mRNA target. The optimal capture probe concentration differs with regard to the different linkers used in the various anthraquinone.-coupled LNA-T capture oligonucleotides. Under the experimental conditions presented here the optimal concentrations were: 25 pmol per microplate well for AQ_2-t15- (SEQ ID NO: 16) and AQ_2-t10-NB5- (SEQ ID NO: 15),

respectively; 50 pmol per well for AQ_2-c15- (SEQ ID NO: 17), and at least 100 pmol per well for AQ_2-HEG_3- linker construct.

Please delete the Table on page 67 and replace it with the following Table:

Table 5. Anthraquinone-coupled LNA-T and DNA (dT) capture probes.

Comp. No.	Oligo Name:	Sequence 5'-:
11	AQ-HEG_3-t20	AQ_2-HEG_3-ttttttttttttttttttt (SEQ ID NO: 1)
12	AQ-HEG_3-2.T	AQ_2-HEG_3-TtTtTtTtTtTtTtTtTtTt (SEQ ID NO: 2)
13	AQ-t15-t20	AQ_2-t15-ttttttttttttttttttt (SEQ ID NO: 11)
14	AQ-t15-2.T	AQ_2-t15-TtTtTtTtTtTtTtTtTtTt (SEQ ID NO: 12)
15	AQ-c15-t20	AQ_2-c15-ttttttttttttttttttt (SEQ ID NO: 13)
16	AQ-c15-2.T	AQ_2-c15-TtTtTtTtTtTtTtTtTtTt (SEQ ID NO: 14)
17	AQ-t10-NB5-t20	AQ_2-t10-NB5-ttttttttttttttttttt (SEQ ID NOS 15 & 1, respectively)
18	AQ-t10-NB5-2.T	AQ_2-t10-NB5-TtTtTtTtTtTtTtTtTtTt (SEQ ID NOS 15 & 2, respectively)

AQ: anthraquinone; HEG: hexa-ethylene glycol; t15 (SEQ ID NO: 16): 15-mer deoxy-thymine; c15 (SEQ ID NO: 17): 15-mer deoxy-cytosine; t10-NB5 (SEQ ID NO: 15): 10-mer deoxy-thymine 5-mer non-base; t: DNA thymine and
T: LNA thymine.

Please delete the paragraph on page 67, lines 10-13, and replace it with the following paragraph:

The AQ-coupled oligo-T capture probes (Table 5[A]) were immobilized onto microplate wells as in the previously example. However, the optimal concentrations of each AQ-linker-LNA-T probe construct were applied (AQ-HEG3-: 100 pmol per well, AQ-c15-(SEQ ID NO: 17): 50 pmol per well, and AQ-t15- (SEQ ID NO: 16) and AQ-t10-NB5- (SEQ ID NO: 15): 25 pmol per well).

Please delete the paragraph on page 67, line 18, to page 68, line 16, and replace it with the following paragraph:

100 nanograms of the *in vitro* polyadenylated *SSA4* spike mRNA was diluted in GuSCN buffer (4 mol/L GuSCN (Sigma, USA), 25 mmol/L sodium citrate (JT Baker), pH 7.0, 0.5 g/100 mL

sodium N-lauroyl sarcosinate (Sigma, USA)). The solution was heated to 65°C 10 minutes and quenched on ice. The polyadenylated *SSA4* mRNA solution was dispersed into the wells by adding 100 ng in 100 µL per well followed by a two-fold dilution series. The final concentrations were 0.87, 3.1, 6.25, 12.5, 25, 50, or 100 ng SSA4 mRNA in 100 µL per well and the samples were incubated for 45 minutes at room temperature. The microtiter wells were washed three times in wash buffer (0.05 mol/L NaCl 20 mmol/L Tris-HCl, pH 7.6, 1 mmol/L EDTA, pH 8, 0.1g/100 mL sodium N-lauroyl sarcosinate). The LNA detection probe (biotin-C_6-AatmCttmCccTtaTcgTtaGtaAttGtaA-tcTtgTt (SEQ ID NO: 39); DNA in lower cases and LNA in upper cases) was diluted to 0.1 µM in 1×SSCT buffer (15 mM sodium citrate, 0.15 M NaCl, pH 7.0, (Eppendorf) 0.1 mL/100 mL Tween 20) and 100 µL was dispersed per well and allowed hybridisation for 30 minutes at room temperature. The wells were washed three times in 1×SSCT buffer and 100 µL per well 1 µg/mL horse radish peroxidase-conjugated streptavidin (Pierce) diluted in 1×SSCT buffer was added to the wells and incubated 15 minutes. The wells were washed three times in 1×SSCT buffer and assayed for peroxidase activity by adding 100 µL of TMB substrate solution (3,3',5,5'-tetramethylbenzidine, Pierce) the reaction was stopped after 3 minutes 30 seconds by adding 100 µL 0.5 M H_2SO_4 and the absorbance at 450 nm was read in a microtiter-plate reader (Wallac Victor^2).

Please delete the paragraph on page 69, line 20, to page 70, line 2, and replace it with the following paragraph:

In an Eppendorf tube 0.5 µg of *in vitro* synthesized, polyadenylated ACT1 mRNA was combined in a final volume of 50 µL DEPC-treated H_2O. 50 µL 2× binding buffer (20 mM Tris-HCl (pH 7.0, Ambion, USA), X M NaCl (Ambion, USA) where X is 0.05, 0.1, 0.2, 0.3, 0.4, or 0.5M NaCl, respectively; and 1 mM EDTA (pH 8.0, Ambion, USA) 0.1% ($^w/_v$) lauryl sarcosinate (Sigma, USA) was added and mixed briefly. The biotinylated LNA oligo(T) capture probe (5'-biotin-C6-TtTtTtTtTtTtTtTtTtTt-3' (SEQ ID NO: 23); T = LNA thymine and t = DNA thymine) was added to the sample preparation together with the pre-blocked streptavidin-coated magnetic particles (preparation described in previous examples) and allowed to hybridize for 10 minutes at 37°C shaking (400 rpm in an Eppendorf Thermomixer (Radiometer, Denmark)). The particles were collected using a magnetic particle separator (Roche, USA) and the supernatant removed. The particles were washed three times in 100 µL wash buffer (20 mM Tris-HCl (pH 7, Ambion, USA),

0.05 M NaCl (Ambion, USA), 1 mM EDTA (pH 8.0, Ambion, USA) 0.1%(w/v) lauryl sarcosinate (Sigma, USA)). Finally, the poly(A)$^+$RNA was eluted form the particles by adding 50 µL DEPC-H_2O (Ambion Cat. no. 9924, USA), heated for 10 minutes at 65°C and quenched on ice for 10 minutes.

Please delete the paragraph on page 71, lines 7-22, and replace it with the following paragraph:

In Eppendorf tubes corresponding to 0, 2.8, 5.5, 11, 22, or 44 mg wet weight *C. elegans* worms, respectively, was mixed in a final volume of 200 µL GuSCN containing buffer (4 M GuSCN (Sigma, USA) in 25 mM Na-citrate (JT Baker), pH 7.0, 0.5 % sodium N-lauroyl sarcosinate (Sigma, USA)) as described in previous examples. To each of the samples 200 pmol biotinylated LNA-T or DNA oligo(T) capture probe (5'-biotin-C_6-TtTtTtTtTtTtTtTtTtTt-3' (SEQ ID NO: 23) or 5'-biotin-C_6-ttttttttttttttttttt-3' (SEQ ID NO: 40); T = LNA thymine and t = DNA thymine) was added together with the pre-blocked streptavidin-coated magnetic particles (described previously) and allowed to hybridize for 10 minutes at 37°C shaking (400 rpm in an Eppendorf Thermomixer (Radiometer, Denmark)). The particles were collected using a magnetic particle separator (Roche, USA) and the supernatant was removed. The particles were washed three times in 100 µL wash buffer (20 mM Tris-HCl (pH 7, Ambion, USA), 0.05 M NaCl (Ambion, USA), 1 mM EDTA (pH 8.0, Ambion, USA) 0.1%(w/v) lauryl sarcosinate (Sigma, USA)). Finally, the poly(A)$^+$RNA was eluted from the particles by adding 50 µL DEPC-H_2O (Ambion Cat. no. 9924), heated for 10 minutes at 65°C and quenched on ice for10 minutes.

Please delete the paragraph on page 71, line 26, to page 72, line 4, and replace it with the following paragraph:

After the mRNA isolation by the LNA oligo(T) capture, 100 ng of polyadenylated RNA was primed with 5 µg oligo-dT_{12-18} primer (SEQ ID NO: 24) (Amersham Biosciences, USA) and heated 10 min at 70°C and quenched on ice. The mixture was transferred to 20 µL first strand cDNA synthesis reaction mixture containing 50 mmol/L Tris-HCl (pH 8.3 at room temperature), 75 mmol/L KCl, 3 mmol/L $MgCl_2$, 10 mmol/L DTT (Invitrogen, USA), 1 mmol/L of each dATP, dCTP, dGTP, and dTTP (Amersham Biosciences, USA), 20U Superasin (Ambion, USA) and incubated for 5 min at 37°C. 200U SuperScript™ II RT (Invitrogen, USA) was added and the reaction mixture was incubated for 30 min at 37°C and 30 min at 42°C. Additional 200U of SuperScript™ II RT were added and the

incubation time at 42°C was prolonged for one hour. Finally, the reaction was heated 5 min at 70°C and primers removed on a Sephacryl S-400 HR spin column (Pharmacia, USA) according to the manufacturer's recommendations.

Please delete the paragraph on page 72, lines 6-20, and replace it with the following paragraph:

The relevant cDNA fragment was amplified from first strand cDNA using a specific primer set for *C. elegans* 26S gene, PCR reactions (50 µL) were prepared by mixing 15 mmol/L Tris-HCl, pH 8.0, 50 mmol/L KCl (GeneAmp Gold buffer, PE Biosystems); 2.5 mmol/L $MgCl_2$; 200 µmol/L of each dATP, dCTP, dGTP and dTTP (Amersham Pharmacia Biotech, USA); 0.4 mmoL/ forward primer (DNA technology, Denmark); 0.4 mmol/L reverse primer (DNA Technology, Denmark); 1.25 U (0.25 µL of a 5U/µl) AmpliTaq Gold polymerase (PE Biosystems, USA) and cDNA as template. After an initial 5 min denaturation step at 95°C, 25 cycles of PCR were carried out (60 s at 95°C, 60 s at 60°C and 60 s at 72°C), followed by extension at 72°C for 10 min. The PCR products were analysed by native agarose gel electrophoresis. The specific primer set was: *C. elegans* 26S rRNA sense 5'-GCCAGAGGAAACTCTGGTGGAAGTCC-3' (SEQ ID NO: 41) and C. elegans 26S rRNA revcom 5'-AGCCTCCCTTGGTGTTTTAAGGGCCG-3' (SEQ ID NO: 42). For Northern blot analysis the PCR amplicons were agarose gel-purified by the QIAEX-II agarose gel extraction kit (Qiagen, USA) according to the protocol provided by the supplier.

Please delete the paragraph on page 73, lines 17-28, and replace it with the following paragraph:

The data obtained by the Northern blot analysis followed by the image analysis quantification (Figure14) demonstrate a 50-fold increase in the isolation of *RPL-21* mRNA when using LNA_2.T compared to the reference DNA-dT_{20} (SEQ ID NO: 1) using the same amount of starting material. In addition, the *C. elegans* poly(A)$^+$RNA samples are highly intact, as revealed by the Northern blot analysis. Since the rRNA ratio in the LNA_2.T and DNA-dT_{20} (SEQ ID NO: 1) purified mRNA samples is significantly lower than the RPL-21 ratio, it can be concluded that the LNA-captured mRNA contains significantly less contaminating rRNA compared to the DNA (dT) control. Combined, these results demonstrate that the LNA oligo(T) capture method results in the isolation of

highly intact poly(A)$^+$RNA in the presence of 4 M GuSCN, in which an extremely potent inhibition of nucleases, including endogeneous RNases and proteases is obtained.

At the last page of the Specification, please insert the Sequence Listing attached hereto and number pages of the sequence listing as appropriate.

Attachment: Paper Copy of Sequence Listing (22 pages).